IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
CLARKSBURG DIVISION

REGENERON PHARMACEUTICALS, INC., Plaintiff, v. MYLAN PHARMACEUTICALS INC., Defendant.	Case No. 1:22-cv-00061-TSK **JURY TRIAL DEMANDED**

REGENERON'S OPENING CLAIM CONSTRUCTION BRIEF

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These proceedings concern aflibercept, the active ingredient in Regeneron's flagship product EYLEA®. Aflibercept works by binding to a protein called "VEGF." VEGF's normal role in the body is to trigger the growth of blood vessels, also known as "angiogenesis." But too much VEGF, and too much resulting blood vessel growth in the eye, can cause vision loss and even blindness. Millions of patients, most of them elderly, suffer from VEGF-related eye diseases, including wet age-related macular degeneration ("AMD") and diabetic macular edema. By binding to VEGF in the eye, aflibercept can treat those and other diseases.

The initial proceedings in this case are focused on three sets of inventions. One patent concerns the "drug product," the actual solution in a vial that maintains the drug's stability for months. Two patents concern aflibercept's use, and specifically, how much and how often the drug should be administered to permit more time between doses than patients enjoyed with previous treatments while achieving therapeutic gains. The final three patents concern methods for making aflibercept arising from Regeneron's efforts to improve how to make the drug.

The parties have identified various claim construction issues, narrowed their disputes through conferral, and memorialized their stipulations and disagreements about the scope of Regeneron's patent rights in the Joint Claim Construction Chart, ECF No. 102. These legal disputes are for the Court to resolve, *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 388-89 (1996), but only "to the extent necessary to resolve the [parties'] controversy" about claim scope, *Vivid Techs., Inc. v. Am. Sci. & Eng'g*, 200 F.3d 795, 803 (Fed. Cir. 1999). The Court should adopt Regeneron's proposed constructions for the reasons set forth below.

I. Legal Principles

Claim construction is the process by which the Court gives legal effect to the meaning of the claims. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 321-22 (2015). "It is not

an obligatory exercise in redundancy" and is not required where a term's meaning is apparent from the claim language itself or its scope is not disputed. *U.S. Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997). "Some line-drawing problems . . . [are] properly left to the trier of fact." *Acumed LLC v. Stryker Corp.*, 483 F.3d 800, 806 (Fed. Cir. 2007).

The Federal Circuit's leading authority on how to construe claims, *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc), instructs district courts to proceed through a canonical hierarchy of evidence: first the claims, then the patent's specification, then its prosecution history, and finally any "extrinsic" evidence. To begin, "[i]t is a 'bedrock principle' of patent law that 'the claims of a patent define the invention.'" *Id.* at 1312. "[T]he claims themselves provide substantial guidance as to the meaning of particular claim terms" and "the context in which a term is used in the asserted claim can be highly instructive." *Id.* at 1314. This is true for both the claim containing the disputed term itself, as well as all other claims in the patent—whether asserted or unasserted. *Id.* "For example, the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim."[1] *Id.* at 1314-15. By the same token, courts should avoid constructions that render a limitation in any claim "redundant," *id.* at 1324-25, or "superfluous," *Mformation Techs., Inc. v. Rsch. in Motion Ltd.*, 764 F.3d 1392, 1399 (Fed. Cir. 2014).

"[T]he words of a claim 'are generally given their ordinary and customary meaning,'" which is "the meaning that the term would have to a person of ordinary skill in the art [("POSA")] in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips*, 415 F.3d at 1312-13. There is a "heavy presumption" that "claim

[1] An "independent" claim is a standalone claim that contains all the limitations that define an invention, whereas a "dependent" claim refers back to, and incorporates by dependency, a previous independent claim and further limits the claim. *See generally* 37 C.F.R. § 1.75.

terms carry their full ordinary and customary meaning." *Epistar Corp. v. ITC*, 566 F.3d 1321, 1334 (Fed. Cir. 2009). Thus, a patentee is "free to choose a broad term and expect to obtain the full scope of its plain and ordinary meaning." *Thorner v. Sony Comput. Ent. Am. LLC*, 669 F.3d 1362, 1367 (Fed. Cir. 2012). A court may depart from that meaning in only two instances: "lexicography" or "disavowal." *Id.* at 1365-66; *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1369 (Fed. Cir. 2012). The lexicography exception applies when a patentee "'clearly set[s] forth a definition of the disputed claim term' other than its plain and ordinary meaning," in the specification or prosecution history, and "'clearly express[es] an intent' to redefine the term." *Thorner*, 669 F.3d at 1365. Disavowal requires the specification or prosecution history unambiguously to make "clear that the invention does not include a particular feature." *Id*.

Beyond the claims themselves, "the specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Phillips*, 415 F.3d at 1315. But while the specification serves as a resource to understand the words used in the claims, courts must avoid the "cardinal sin" of importing language from the specification into the claims. *Id.* at 1320. Indeed, even if every example described in the specification contains a particular element, such uniformity is *not* enough to justify importing that element into claims whose plain language does not expressly require it. *See id.* at 1323; *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906-07 (Fed. Cir. 2004).

"[A] court 'should also consider the patent's prosecution history.'" *Phillips*, 415 F.3d at 1317. "Yet because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes." *Id.*

Sometimes, a "court will need to look beyond the patent's intrinsic evidence and to

consult extrinsic evidence in order to understand, for example, the background science or the meaning of a term in the relevant art during the relevant time period." *Teva Pharm.*, 574 U.S. at 331. When claim construction "involves little more than the application of the widely accepted meaning of commonly understood words[,] . . . general purpose dictionaries may be helpful." *Phillips*, 415 F.3d at 1314. But extrinsic evidence cannot be used to "contradict claim meaning that is unambiguous in light of the intrinsic evidence." *Id.* at 1318-19, 1324.

II. The Formulation Patent

U.S. Patent No. 11,084,865 (Ex. 1) claims an EYLEA drug product, *i.e.*, a "vial" containing an "ophthalmic formulation" that is "suitable for intravitreal administration." '865 patent, claim 1. "[I]ntravitreal administration" refers to how the formulation is injected into the eye. As relevant here, EYLEA is injected into the vitreous and diffuses into the back of the eye—where the retina is located and where aflibercept is therapeutically active. The claimed ophthalmic formulation comprises several components: a VEGF antagonist[2] with a specific sequence,[3] "an organic co-solvent," a buffer, and a stabilizing agent. The claim further requires that the formulation possess a particular type of stability measured in a specific way: at least 98% of the VEGF antagonist must be "present in native conformation following storage at 5° C. for two months *as measured by size exclusion chromatography*."

The parties have two disputes with respect to the '865 patent: what constitutes an "organic co-solvent" and what it means for the aflibercept to be "present in native conformation . . . as measured by size exclusion chromatography."

[2] Compounds that bind to and counteract VEGF are known as "VEGF antagonists."

[3] The limitation "amino acids 27-457 of SEQ ID NO:4" describes the "amino acid sequence" of the VEGF antagonist and corresponds to the sequence of the aflibercept protein.

A. "Organic Co-Solvent"

Regeneron's Proposed Construction	Mylan's Proposed Construction
Plain and ordinary meaning in view of the claims and specification; to the extent there is a dispute as to claim scope, "organic co-solvent" includes polysorbate 20, polysorbate 80, polyethylene glycol, or propylene glycol, or a combination thereof	an organic substance added to a primary solvent to increase the solubility of said VEGF antagonist

The parties dispute whether the substances specifically listed in the patent as "organic co-solvents" are in fact "organic co-solvents." Under Mylan's proposal, despite being specifically listed as "organic co-solvents" in the claims and specification, these substances somehow could be excluded from the scope of that term. But the claims and specification leave no doubt that the listed substances like polysorbate are "organic co-solvents."

The dependent claims resolve this dispute, expressly claiming that the "organic co-solvent" is "polysorbate." "[D]ependent claims can aid in interpreting the scope of claims from which they depend," *Laitram Corp. v. NEC Corp.*, 62 F.3d 1388, 1392 (Fed. Cir. 1995), because independent claims necessarily must cover the entirety of the subject matter of claims that depend from them. *See Curtiss-Wright Flow Control Corp. v. Velan, Inc.*, 438 F.3d 1374, 1380 (Fed. Cir. 2006) ("[T]he statute stresses that a dependent claim must *add* a limitation to those recited in the independent claim." (emphasis added) (citing 35 U.S.C. § 112, ¶ 4 (now § 112(d)))). In *Laitram*, for example, the Federal Circuit reasoned that because a dependent claim recited a particular embodiment (a printer that "strobes"), that embodiment must also be covered by the broader independent claim. *Id.* at 1392-93. The same result obtains here: claim 2 depends from claim 1 and recites specifically that "said organic co-solvent comprises polysorbate"; claims 4-5 depend from claim 2 and more specifically recite that "said organic co-solvent" comprises an amount of "polysorbate 20." It thus follows as a matter of law that the

"organic co-solvent" in claim 1 must include polysorbate (and more).

The specification reinforces this point. As "the single best guide to the meaning of a disputed term," *Phillips*, 415 F.3d at 1315, its guidance here is unequivocal: "the organic co-solvent may be polysorbate, for example, polysorbate 20 or polysorbate 80, polyethylene glycol (PEG), for example, PEG 3350, or propylene glycol, or a combination thereof." '865 patent, 2:39-42. Though once would be enough, the specification repeatedly confirms that substances like polysorbate are organic co-solvents. '865 patent, 2:39-40, 2:49-50, 3:28-30, 4:16-17, 7:5.

Resolving the parties' claim construction dispute concerning "organic co-solvent" thus requires no more than acknowledging what the claims and specification state clearly: polysorbate is an organic co-solvent. Courts construe claims "only to the extent necessary to resolve the [parties'] controversy," which is whether "organic co-solvent" includes or excludes polysorbate, and there is no need for the Court to consider what additional substances this claim term encompasses [redacted]. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017). While the Court must construe the claims "objectively" in view of the intrinsic record "and without reference to the accused device," the parties have a simple dispute as to claim scope—whether polysorbate, one of the specification's listed organic co-solvents, is within the meaning of "organic co-solvent." *Vivid Techs., Inc.*, 200 F.3d at 803. Mylan's [redacted] explains why the parties contest the meaning of "organic co-solvent" and essentially frames the dispute requiring the Court's resolution.

Mylan contends that whether polysorbate is an organic co-solvent depends on why and how it was added to the formulation. This construction defies the patent's repeated and unequivocal guidance—the words of Mylan's construction are found nowhere in the

specification. "The only meaning that matters in claim construction *is the meaning in the context of the patent*," and the patent could not be clearer that polysorbate is an organic co-solvent. *Tr. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1363 (Fed. Cir. 2016) (emphasis added). To the extent Mylan seeks to rely on extrinsic evidence to the contrary, such evidence cannot trump the claims' and specification's clear guidance. *Phillips*, 415 F.3d at 1318.

Further, while the claim language and specification suffice to end the inquiry, Mylan's proposed construction suffers additional defects. Under Mylan's proposed construction, a substance would only count as an "organic co-solvent" if it satisfies two functional requirements: that the organic co-solvent (1) is "added to a primary solvent," (2) "to increase the solubility of said VEGF antagonist." Neither requirement finds any support in either the plain language of the claims or the specification, and both are contrary to Federal Circuit precedent.

First, the specification nowhere teaches that an organic co-solvent must be "added to a primary solvent"—indeed, the patent never uses the phrase "primary solvent" at all. And in most of the examples (1, 3-8), polysorbate is the only organic co-solvent. '865 patent, 8:33-12:13. If, as Mylan contends, polysorbate is *not* an organic co-solvent, then each of these embodiments is not covered by the patent. But "a claim interpretation that excludes a preferred embodiment from the scope of the claim is rarely, if ever, correct." *CUPP Comput. AS v. Trend Micro Inc.*, -- F.4th --, 2022 WL 16954357, at *3 (Fed. Cir. Nov. 16, 2022). It is surely incorrect here.

Second, the specification nowhere suggests that an "organic co-solvent" must "increase the solubility of said VEGF antagonist." Under Mylan's construction, a substance would be an "organic co-solvent" in some circumstances but not in others. That is contrary to the term's usage in the specification, which simply lists examples of substances that are organic co-solvents generally, without evaluating whether those substances increase the solubility of a VEGF

antagonist in a particular formulation. '865 patent, 2:39-42, 3:28-31, 4:15-17, 7:5-7. In this respect, Mylan's proposed construction violates (another) principle of claim construction by introducing confusion and uncertainty into the meaning of a claim term where it otherwise would not exist. As the Federal Circuit has explained, the core purpose of claim construction is "to clarify" claim scope, *U.S. Surgical*, 103 F.3d at 1568, so that "the finder of fact [has] an understandable interpretation of claim scope to apply to the accused [product]," *Avid Tech., Inc. v. Harmonic, Inc.*, 812 F.3d 1040, 1050 (Fed. Cir. 2016). By inventing a functional test nowhere disclosed in the specification that would make a substance an "organic co-solvent" for some formulations but not for others, Mylan's proposed construction confounds rather than clarifies.

B. "Present in Native Conformation . . . as Measured by Size Exclusion Chromatography"

Regeneron's Proposed Construction	**Mylan's Proposed Construction**
This term does not need to be construed outside of the context of the limitations in which it appears (e.g., "wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography."). Within that context, it should be given its plain and ordinary meaning in view of the claims and the specification	Plain and ordinary meaning: *[present in] a form that does not exhibit chemical or physical instability*

The Court should construe the phrase "present in native conformation" in the context of the limitation in which it appears, which recites specifically that the VEGF antagonist is "present in native conformation following storage at 5° C. for two months *as measured by size exclusion chromatography*." '865 patent, claim 1 (emphasis added). The complete claim language instructs the reader how to determine whether the VEGF antagonist is "present in native conformation," and no further construction is necessary. Mylan's proposed construction is wrong for two reasons: (1) it obscures the specific way in which "native conformation" is

measured in the '865 patent, and (2) it introduces a vague functional limitation encompassing unspecified types of "chemical or physical []stability" that are not recited in the claims and would not be measured by size exclusion chromatography.

The claim construction inquiry "must begin and remain centered on the language of the claims themselves." *Interactive Gift Exp., Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001); *Phillips*, 415 F.3d at 1314. And in interpreting the claim language, "the context of the surrounding words of the claim . . . must be considered in determining the ordinary and customary meaning of those terms." *Phillips*, 415 F.3d at 1314 (quoting *ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003)). That context here is essential, because it specifies precisely how "native conformation" is "measured": by "size exclusion chromatography." '865 patent, claim 1. In view of this context, "present in native conformation" does not require further construction. Mylan, in contrast, seeks to construe "native conformation" in isolation from the surrounding claim language and as requiring various types of stability untethered to the particular assay recited in the claims. That would be error.

Contrary to Mylan's proposed construction, the claims do not recite that "native conformation" is a catch-all phrase relating to all forms of "chemical and physical instability." Nor does the specification. Although the '865 patent provides a "general description" explaining that proteins may exhibit both "[c]hemical instability" and "[p]hysical instability," the specification does not equate these general concepts to the claimed "native conformation" measured by size exclusion chromatography. '865 patent, 5:51-60. The specification does not even mention "native conformation" in this passage. *Id.* Rather, it explains that there are multiple attributes of protein stability, '865 patent, 5:51-60, and various methods for evaluating different aspects of protein stability, *id.* at 7:8-19 (listing, among others, "UV spectroscopy,"

"SDS -PAGE," and "isoaspartate quantification"). But these various stability attributes and means for assessing them are absent from the claims, which recite neither "chemical" nor "physical" stability. Claim 1 recites just *one* attribute and *one* measurement technique: that the VEGF antagonist is "present in native conformation . . . as measured by size exclusion chromatography." "[S]ize exclusion chromatography" does not measure all types of stability—rather, it is a technique used specifically to separate molecules of different size.[4] Size exclusion chromatography is used to separate "native proteins" from "aggregated proteins," *i.e.*, significantly larger clumps formed by several proteins sticking together. Roufik at 235. That is how size exclusion chromatography is used in the '865 patent—to detect the amount of protein in "native" conformation. But the technique has limitations: "A 50–100% difference in molecular weight is typically required" for separation by size exclusion chromatography. Goetz at 287. The types of instability that Mylan's construction attempts to smuggle into the claims, such as "deamination" and "oxidation of methionine residues," '865 patent, 5:57-58, refer to minute changes in the structure of the protein that are not detectable by size exclusion chromatography. Mylan's construction thus makes no sense, as it encompasses changes to the VEGF protein that are not detected by the analytical technique expressly referenced in the claim.

The specification's disclosure relevant to "native conformation" does not refer to "physical" or "chemical" instability generally. Rather, the patent explains that size exclusion chromatography (specifically, "size exclusion HPLC") was used to evaluate the VEGF antagonist's "purity," which the patent refers to in data tables as "% VEGF Trap Native

[4] Ex. 7, H. Goetz et al., *Comparison of Selected Analytical Techniques for Protein Sizing, Quantitation and Molecular Weight Determination*, 60 J. Biochem. Biophys. Methods 281, 287 (2004) ("Goetz"); Ex. 8, S. Roufik et al., *Use of High-Performance Size Exclusion Chromatography to Characterize Protein Aggregation in Commercial Whey Protein Concentrates*, 15 Int'l Dairy J. 231, 232 (2005) ("Roufik").

Configuration" and in the claims as "native conformation." *E.g.*, '865 patent, 8:42-44, Table 1, claim 1.[5] The claims require that "*at least 98%* of the VEGF antagonist is present in native conformation following storage at 5°C. *for two months*," and that is precisely what the patent's data tables show: size exclusion chromatography data from aflibercept formulations with native conformation of greater than 98% for at least two months. *See* '865 patent, Table 1 (98.7% at 3 months), Table 2 (98.5% at 3 months), Table 3 (99.2% at 2 months), Table 4 (99.1% at 2 months), Table 5 (99.2% at 2 months), Table 6 (99.1% at 3 months), Table 7 (99.3% at 2 months), Table 8 (98.9% at 2 months). By reading into the claims concepts of stability that are not measurable by size exclusion chromatography as required by the claims, Mylan's proposed construction commits the "cardinal sin[] of patent law" by "reading a limitation from the written description into the claims." *Phillips*, 415 F.3d at 1320 (quoting *SciMed*, 242 F.3d at 1320).

The prosecution history of the '865 patent—"the complete record of the proceedings before the PTO" in examining the patent—further demonstrates that it was these data and related descriptions that underpin these claims, not general descriptions of physical and chemical stability. *Phillips*, 415 F.3d at 1317. When Regeneron filed the application that ultimately issued as the '865 patent, it submitted claims reciting the "present in native conformation" limitation. Ex. 9, Applicant Remarks, Amendments to the Claims at 2 (Jan. 10, 2020). Regeneron identified for the Examiner where its disclosure supported the claims, directing the Examiner to, *inter alia*, "example 6"—one of the formulations that achieved at least 98% native conformation after two months—not to the "General Description" of protein stability.

In short, "present in native conformation" means no more and no less than what the

[5] Size exclusion chromatography was also used to measure another property, the "% VEGF Trap Recovered," which is not recited in the claims or as part of either party's construction of "present in native conformation." '865 patent at 8:42-44, Table 1.

claims expressly say and what the patent's examples plainly demonstrate: it is a property measured by size exclusion chromatography. The Court should not insert any other stability criteria. And more specifically, the Court should not accept Mylan's request to import stability requirements into the claims that cannot be measured by size exclusion chromatography and thus would render the claims nonsensical. As with "organic co-solvent," Mylan's proposed construction here again only add confusion to these proceedings and should be rejected. *See U.S. Surgical*, 103 F.3d at 1568.

III. The Treatment Patents

U.S. Patent Nos. 10,888,601 (Ex. 2) and 11,253,572 (Ex. 3) claim methods of using aflibercept to treat eye disorders involving abnormal angiogenesis. The methods of treating angiogenic eye disorders addressed in the '601 and '572 patents include dosing and patient assessment and treatment regimens for using aflibercept to treat wet age-related macular degeneration and other angiogenic eye disorders, such as diabetic macular edema and central retinal vein occlusion.

After inventing aflibercept itself, Regeneron began a substantial clinical program to study how best to use it. One of Regeneron's founders and leading scientists, Dr. George Yancopoulos, innovated methods of treating patients with aflibercept that extended the time between doses without sacrificing efficacy—longer than had been achieved for any other "VEGF antagonists" such as Lucentis® or Macugen®, and longer than anyone expected could be achieved with aflibercept. This is a significant benefit for patients because aflibercept is administered at the ophthalmologist by injection into the eye. While patients tolerate such injections to stop or reverse blindness or vision loss, they understandably prefer to minimize the number of injections into their eyes. And most of the population afflicted with age-related

macular degeneration is elderly, for whom monthly doctor visits can be very burdensome.

Regeneron's method-of-treatment inventions enable patients to have less frequent injections than FDA had approved for earlier VEGF antagonists. Claim 1 of the '572 patent is illustrative of the method-of-treatment claims at issue. Its method begins with the administration to a patient of 2 mg of aflibercept, followed by one or more secondary doses spaced four weeks apart, followed by one or more tertiary doses spaced eight weeks apart, with associated visual acuity gains within 52 weeks. '572 patent, claim 1.

The parties do not dispute the meaning of any terms that appear in the independent claims. Rather, their disputes concern the scope of certain dependent claims that add further limitations to the treatment methods, including the means of assessing patient visual gains through Best Corrected Visual Acuity ("BCVA") scores; the exclusion of certain patients from treatment based on ocular inflammation or infection; and the method of administering aflibercept using an "isotonic solution." ECF No. 102 at 2-3, 9, 13-15.

A. "Best Corrected Visual Acuity"

Several claims in the '601 and '572 patents require assessing the patient's gains in visual acuity through the use of a "BCVA" analysis. The parties propose to construe that term as follows:

Regeneron's Proposed Construction	**Mylan's Proposed Construction**
the best visual acuity that can be achieved with the use of a corrective lens	Plain and ordinary meaning: Best Corrected Visual Acuity (BCVA), measured in letters, a clinical trial endpoint / measurement

Although the parties' constructions use different words, the conferral process suggested their disputes are narrow. Mylan does not appear to dispute that "Best Corrected" vision refers to the best vision that can be achieved using a corrective lens. And Mylan appears to agree that BCVA describes measuring a vision outcome for the patient, in contrast to an anatomical

outcome like the amount of fluid in the patient's eye. The parties further appear to agree that BCVA can be measured through letter scores obtained by having patients read letter charts.

Regeneron understands the parties to have only one real dispute: Mylan's outcome-driven argument that "BCVA" can only refer to a "clinical trial endpoint/measurement," and not the assessment of patients outside of trials. Nothing in the claim language refers to clinical trials, and the notion that Regeneron would patent methods limited to the performance of clinical trials is absurd because such activities are, by statute, typically immune from patent infringement. *See* 35 U.S.C. § 271(e)(1). Regeneron did not seek and obtain claims directed to methods that cannot be infringed and have no commercial consequence, and the Court should decline to adopt such an absurd construction. *Ortho-McNeil Pharm., Inc. v. Mylan Lab'ys, Inc.*, 520 F.3d 1358, 1362-63 (Fed. Cir. 2008) (rejecting absurd construction in favor of what patentee intended).

Mylan's proposed construction of BCVA to limit the claims to performing clinical trials is not only contrived—it has no basis whatsoever in the intrinsic record. The surrounding claim language—critical intrinsic evidence under the *Phillips* rubric—confirms that the claims are directed to treating "*patients*," not clinical trial subjects.[6] Individuals who receive treatment in a clinical trial are subjects; the term "patients" is not so limited, and, accordingly, the claims are not so limited either. Illustrating this distinction, claims 26 and 29, when addressing a comparison between the efficacy of (1) the claimed method and (2) a clinical trial involving Lucentis® (ranibizumab), use "patients" to refer to the former and "subjects" to refer to the

[6] *See* Ex. 10 (Govani et al., *How To Read a Clinical Trial Paper*, Gastroenterol Hepatol (N Y). 2012 Apr. 8(4): 241–248) at 242 ("The first step in the process of reviewing a trial should involve determining whether the *subjects* in the study are representative of the *patients* a clinician sees in his or her practice . . . . Compared to the average *patient*, study *subjects* often have a longer duration of disease, more complications, more active disease, and more previous medication failures." (emphases added)); *see, e.g.*, '572 patent, claims 26, 29 (referencing "subjects" in contrast to "patients" as a comparison population).

latter. Thus, the claimed methods, including the use of BCVA, explicitly are not limited to the clinical trial context. That the claims specify treating *patients* forecloses Mylan's argument.

Mylan's position also is inconsistent with the specification, the "single best guide" to understanding the claims. *Phillips*, 415 F.3d at 1315. From start to finish, the specification makes clear that it is directed to the treatment of patients who present with eye disorders, and not merely the testing of aflibercept on clinical trial subjects. The very title of the patents says they are directed to "Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders." In the section titled "Treatment Population and Efficacy," the specification discloses that "[t]he methods of the present invention are useful for treating angiogenic eye disorders in patients that have been diagnosed with or are at risk of being afflicted with an angiogenic eye disorder." '601 patent, 7:26-30. If Mylan were correct that the invention is limited to the clinical trial context, the specification would not discuss repeatedly the treatment of patients. *See* '572 patent, 2:13-14 ("The present invention provides methods for *treating* angiogenic eye disorders." (emphasis added)); 2:21-25 ("The present inventors have surprisingly discovered that beneficial *therapeutic effects* can be achieved in *patients suffering from* angiogenic eye disorders . . . ." (emphases added)). The specification even emphasizes that "Aflibercept (EYLEA™, Regeneron Pharmaceuticals, Inc) was approved by the FDA in November 2011, *for the treatment of patients*[.]" '572 patent, 2:61-63 (emphasis added). And while the patents' *examples* present data from various clinical trials, the rest of the specification makes clear that these data provide the basis for an invention of treating *patients*. *See*, *e.g.*, '572 patent, 2:47-48 ("The methods of the present invention comprise administering any VEGF antagonist to the patient."); 4:22-23 ("The methods of the invention may comprise administering to a patient . . . ."); 6:50-51 ("Each dose of VEGF antagonist administered to the *patient* over the course of the *treatment regimen*

. . . ." (emphases added)). The prosecution history similarly emphasizes the need for treating patients, not conducting clinical trials. Ex. 11, Applicant Remarks, Amendments to the Claims at 5-6 (Jan. 30, 2017) (applicant remarks describing need for improved treatment of patients).

Mylan's litigation-driven proposal to limit these claims to performing clinical trials is inconsistent with its own prior statements. In July 2022, Mylan filed a Petition for *inter partes* review of the '601 patent with the Patent Trial and Appeal Board ("PTAB") directed to the '601 patent, alleging that its claims would have been obvious to *practicing ophthalmologists treating patients*. Ex. 12. Mylan's arguments in that filing did not remotely cast the claims as limited to treatment during clinical trials. To the contrary, Mylan argued that the '601 patent's methods would have been obvious because "of the risks and financial burden of monthly intravitreal injections," *id.* at 2—concepts applicable to patients, but not to clinical study subjects. Mylan argued that the '601 patent "broadly claims" the regimen that "became the FDA-approved regimen for EYLEA®," *id.* at 14—a regimen approved for use by ophthalmologists treating patients. Mylan also argued that the '601 patent claims would have been obvious due to the POSA's purported motivation to solve a "known problem in treating AMD," and that existing monthly dosing was a "'significant' drawback to then-existing AMD therapy." *Id.* at 60. Again, these concepts relate to treating *patients* outside the clinical trial context. Mylan's challenge included a Declaration by its proffered expert, Dr. Thomas Albini, who testified that: "The '601 patent pertains to dosing regimens for treating angiogenic eye disorders, including AMD, in patients." Ex. 13, ¶ 38. Dr. Albini opined that the phrase "method of treating," used in both the '601 and '572 patents, refers to "administering a therapeutic agent to a patient." *Id.* ¶ 47.

While Regeneron disagrees with Mylan's invalidity arguments to the PTAB, one thing is clear: Mylan has written extensively about Regeneron's claims as methods for treating

angiogenic eye disorders in practice rather than simply in clinical trials, because it is plain that the claims are not limited to the clinical trial context.

B. Patients Excluded from Treatment

Injecting aflibercept risks spreading infection into the eye, and so various claims include the further limitation, "wherein exclusion criteria for the patient include both of: (1) active ocular inflammation; and (2) active ocular or periocular infection." The parties have two disputes about this limitation: (1) what it means; and (2) whether it is a limitation. *See* ECF No. 102 at 13-14.

Regeneron's Proposed Construction	**Mylan's Proposed Construction**
"assessing the patient for (1) active ocular inflammation; and (2) active ocular or periocular infection, and administering aflibercept to the patient on the basis of the foregoing assessment." The "patient" is not limited to a clinical trial subject.	"wherein exclusion criteria for the patient to be eligible in the clinical study of the said method for treating include"

1. "Exclusion criteria" refer to bases for not administering aflibercept to a patient. Applying exclusion criteria necessitates assessing the patient for those criteria and administering the drug based on that assessment. Regeneron's proposed construction tracks the plain meaning of the claim language and should be adopted.

Mylan's construction, on the other hand, again attempts to limit various claims to the clinical trial setting. Its argument is as incorrect here as it was with "BCVA." As discussed above, these patents and claims are directed to therapeutic treatment of patients who have angiogenic eye disorders. *See supra* III.A. The specification provides that the dosing "administered to a patient" may be varied "based on *patient* characteristics, severity of disease, and *other diagnostic assessments* by a physician[.]" '601 patent, 17:11-15 (emphases added).

Mylan's IPR submissions again demonstrate that it understands perfectly well that excluding patients from treatment if certain infection and inflammatory conditions are present is

a step that occurs in connection with the *treatment of patients*. In that proceeding, Mylan's Dr. Albini discussed the practice of assessing patients in practice for ocular and inflammatory conditions. Ex. 13. He described literature relating to the exclusion of patients from various treatment options, and then opined that "[i]t was . . . well understood that some *patients should be excluded from treatment* administered via intravitreal injection, particularly those patients at increased risk for infection or inflammation." *Id.* ¶ 93 (emphasis added) (citing Heimann-2007, here Ex. 14). He further opined that "[t]he exclusion of patients with, for example, uveitis (a form of intraocular inflammation) from methods of treatment involving intraocular injections was known[.]" *Id.* Dr. Albini's testimony, submitted by Mylan, makes clear that the patent's exclusion criteria apply to the treatment setting, not only the clinical trial setting, and there is simply no basis to read "clinical study" limitations into the claim where the claim language makes no mention of the concept. *Phillips*, 415 F.3d at 1320.

2. If it cannot rewrite this claim limitation to its liking, Mylan's alternative proposal is that the exclusion criteria are not claim limitations at all, invoking the so-called "printed matter" doctrine. The "printed matter" doctrine relates to method steps that are directed to "providing information" or that "claim[] the content of information" without a further adjustment in the physical method. *See, e.g., Praxair Distribution, Inc. v. Mallinckrodt Hosp. Prods. IP Ltd.*, 890 F.3d 1024, 1032, 1037 (Fed. Cir. 2018) (holding claims 9's limitation that required adjustment in treatment had patentable weight); *In re Distefano*, 808 F.3d 845, 848-51 (Fed. Cir. 2015). The doctrine is meant to prevent parties from claiming basic non-patentable subject matter such as "purely mental steps, naturally occurring phenomena or laws of nature, [or] a mathematical formula and the algorithm therefor." *See In re Chatfield*, 545 F.2d 152, 157 (CCPA 1976) (citations and quotations omitted). To determine whether a claim limitation runs

afoul of the "printed matter" doctrine, courts evaluate whether (1) a claim limitation is directed to printed matter and, if so, (2) whether the limitation is nonetheless entitled to patentable weight because it is functionally related to the rest of the claim. *Praxair*, 890 F.3d at 1032. Where an assessment or information affects an actual step of a claimed method, such as whether or how to administer a drug, the limitation does have patentable weight, *CR Bard Inc. v. AngioDynamics, Inc.*, 979 F.3d 1372, 1381 (Fed. Cir. 2020); *Praxair*, 890 F.3d at 1035, and such treatment methods have been squarely deemed patentable subject matter, *Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117, 1135 (Fed. Cir. 2018) (method of treating patient based on genotype held patentable).

The claims at issue here do not incorporate any "printed matter" and, even if they did, the exclusion criteria are functionally related to the rest of the claim, because they define the population that is to be treated. The specification explains that methods of treating patients may vary based on the condition of the patient, after a "physician or other qualified medical professional" makes a "diagnostic assessment[]." *See* '601 patent, 17:11-15. Patients do not come to doctors pre-screened for infection or inflammation, and Mylan cannot suggest that they do. The reference to "exclusion criteria" would be rendered superfluous if it were not meant to be acted upon as a limitation of the method claimed. *Mformation Techs., Inc.,* 764 F.3d at 1399. And it is well-established that limitations defining the population of patients to be treated are, in fact, limiting. *E.g., Rapoport v. Dement*, 254 F.3d 1053, 1058-60 (Fed. Cir. 2001). The specification and claims make clear that the act of making "diagnostic assessments" is within the scope of the invention and that these dependent claims add a step to the claimed methods of assessing patients to determine whether some should be excluded.

The Federal Circuit's *Praxair Distribution, Inc*., case is instructive. There, the method

claim at issue contained several components, including providing information and a recommendation to the health care provider to cease nitric oxide treatment to patients who experienced pulmonary edema, and then "based on" the recommendation, "discontinuing" the treatment due to the pulmonary edema. *Id.* at 1035. The defendant argued that these limitations ran afoul of the printed matter doctrine and should be held not to have patentable weight. The Court disagreed, explaining that the claim required a medical provider to "take a specific action, discontinuing treatment, as a result of the recommendation limitation." *Id.* The claims at issue here provide precisely the same functional relationship between the assessment for specified conditions (infection or inflammation) and exclusion of certain patients from treatment.

C. "Formulated as an Isotonic Solution"

The last dispute regarding the Treatment Patents concerns the phrase "formulated as an isotonic solution" in claims 6, 12, 18, and 22 of the '572 patent. The parties disagree about whether this solution must contain glucose, although the dispute is not well-crystallized in the Joint Chart. ECF No. 102 at 9. Mylan identified this term as needing construction and proposed that the isotonic solution must "contain glucose." Regeneron disagreed, emphasizing the absence of any language reciting glucose in the claims. Mylan then urged this term does not need to be construed, but also refused to stipulate to Regeneron's position that "isotonic solution" does not require glucose. *Id.*; Ex. 15 (Nov. 16, 2022 Mylan Email). The parties therefore have a dispute as to claim scope, and the Court "must resolve that dispute." *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.*, 521 F. 3d 1351, 1360 (Fed. Cir. 2008).

"Isotonic" refers to the osmotic pressure of a solution, which is determined by the concentration of solutes in the solution. *See* Ex. 16 (*Isotonic*, *The New Oxford American Dictionary* (2d ed. 2005)) ("denoting or relating to a solution having the same osmotic pressure

as some other solution, esp. one in a cell or a body fluid."); Ex. 17 (*Isotonic*, *The American Heritage Dictionary of the English Language* (4th ed. 2006)) ("[h]aving the same concentration of solutes as the blood: *an isotonic saline solution*."); Ex. 18 (*Isotonic*, *Webster's New World College Dictionary* (4th ed. 2004)) ("having the same osmotic pressure; esp., designating or of a salt solution having the same osmotic pressure as blood"). The plain meaning of "isotonic solution" does not require glucose to be present in the solution, as opposed to other solutes.

Mylan's construction that reads a limitation into the plain meaning of "isotonic solution" thus can be correct only if the patentee redefined "isotonic" in the specification or disclaimed its ordinary meaning. *Toshiba Corp.*, 681 F.3d at 1369. But there is neither a definition nor a disclaimer in the specification or prosecution history. The specification simply lists glucose as an example of an ingredient in one isotonic solution, along with "other auxiliary agents":

> As the aqueous medium for injections, there are, *for example,* physiological saline, *an isotonic solution containing glucose and other auxiliary agents*, etc., which may be used in combination with an appropriate solubilizing agent . . . .

'572 patent, 6:22-30 (emphases added). This passage comes nowhere close to an attempt to define comprehensively what an "isotonic solution" must contain. It is well established that claims are not limited to the specification's examples. "[E]ven if all of the embodiments discussed in the patent included a specific limitation, it would not be proper to import from the patent's written description limitations that are not found in the claims themselves." *Cadence Pharmaceuticals Inc. v. Exela Pharmsci Inc.*, 780 F. 3d 1364, 1369 (Fed. Cir. 2015). Thus, the inclusion of "glucose" as an example of a solute in an isotonic solution cannot, as a matter of law, justify departure from the ordinary meaning of "isotonic" to require that the claimed methods use formulations containing glucose.

IV. The Manufacturing Patents

While Regeneron has been making and selling EYLEA since 2011, it has continued to investigate ways to improve its manufacturing processes. U.S. Patent Nos. 11,104,715, 11,053,280, and 11,299,532 (Exs. 4-6, "the Manufacturing Patents") describe and claim new methods of making aflibercept using a particular type of ingredient known as a "chemically defined medium" or "CDM."

Aflibercept is produced by genetically engineered cells. *See* '715 patent, 33:3-6. These cells are grown in a specialized vat in liquid containing various chemicals and nutrients. This process is referred to as "cell culture." *See* '715 patent, 55:24-37. These cells make aflibercept and secrete it into the liquid, which is then "harvested." '715 patent, 55:49-52.[7]

The parties' three claim construction disputes relate to these processes. The first two disputes concern the ingredients used, while the third concerns the nature of the process.

A. "Anti-oxidants"

Claim 1 of the '715 patent describes a process for making aflibercept involving a "CDM." '715 patent, 261:2-23. Among other things, the CDM of claim 1 may contain "anti-oxidants." *Id.*, 261:20-22. The parties disagree about what these anti-oxidants can be, though the dispute is not well-crystallized in the Joint Chart. ECF No. 102 at 7-9. Similar to the parties' dispute regarding "isotonic solution," Mylan identified this term as one needing construction. It proposed that "anti-oxidants" are limited to "taurine, hypotaurine, glycine, thioctic acid, glutathione, choline chloride, hydrocortisone, Vitamin C, Vitamin E and combinations thereof." Regeneron disagreed, pointing to the fact that two dependent claims provide that list while the

[7] Figure 59 of the '715 patent outlines a typical manufacturing process. For additional background on using genetically engineered cells to make biologic drugs, see J.R. Birch & A.J. Racher, *Antibody Production*, 58 Adv. Drug Delivery R. 671 (2006) (Ex. 19).

specification discloses a longer list of potential anti-oxidants. '715 patent, claims 3, 12, 23:67-24:1. Mylan then urged this term does not need to be construed, but also refused to stipulate to Regeneron's position. ECF No. 102 at 7-9; Ex. 15 (Nov. 16, 2022 Mylan Email). The parties therefore have a dispute that the Court "must resolve." *O2 Micro*, 521 F.3d at 1360.

Mylan's suggestion that the "anti-oxidants" that can be added to the CDM are limited to the list recited above violates two core principles of claim construction: claim differentiation and a presumption against narrowing a term's ordinary meaning. The Court should hold that the claimed method permits the use of any anti-oxidant, not just those on Mylan's list.

First, the plain language of claim 1 refers to "anti-oxidants," not to Mylan's list. Dependent claim 3, however, *does* require the use of an anti-oxidant from Mylan's list. The doctrine of "claim differentiation" presumes that an independent claim has a different, broader scope than its dependent claim. *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1374 (Fed. Cir. 2014). The presence of Mylan's list in dependent claim 3 gives rise to the presumption that claim 1 is not so limited. *Phillips*, 415 F.3d at 1315; *see Littelfuse, Inc. v. Mersen USA EP Corp.*, 29 F.4th 1376, 1380 (Fed. Cir. 2022); *Intamin Ltd. v. Magnetar Techs., Corp.*, 483 F.3d 1328, 1335 (Fed. Cir. 2007). Indeed, Mylan's proposed construction would render claim 3 superfluous. The Federal Circuit has made clear that a construction like Mylan's is "highly disfavored." *See Intel Corp. v. Qualcomm Inc.*, 21 F.4th 801, 810 (Fed. Cir. 2021).

Second, Mylan's proposal also violates the presumption that claim terms should not be narrowed unless the patentee (1) redefines the term in the patent specification, or (2) disavows the full scope of the term either in the specification or during prosecution. *Thorner*, 669 F.3d at 1365-66. Mylan cannot meet either test. Nothing in the patent's specification narrows the breadth of "anti-oxidants." To the contrary, it discloses a list of "[n]on-limiting examples of the

antioxidant." '715 patent, 23:64-24:3. Critically, that "non-limiting" list includes chemicals like "S-carboxymethyl-L-cysteine" and "chelating agents" like "aurintricarboxylic acid" and "citrate." *Id.* Mylan's proposed construction excludes these chemicals even though the specification includes them as examples of "antioxidant[s]." Mylan's attempt to read a limitation into the claims is simply improper. *E.g.*, *Trebro Mfg., Inc. v. FireFly Equip., LLC*, 748 F.3d 1159, 1166-67 (Fed. Cir. 2014).

B. "Chemically Defined Medium (CDM)"

Regeneron's Proposed Construction	**Mylan's Proposed Construction**
a synthetic growth medium in which the identity and concentration of all the ingredients are defined	a synthetic growth medium in which the identity and concentration of all the ingredients are defined *and does not contain bacterial, yeast, animal, or plant extracts or hydrolysates, animal serum, or plasma*

Each of the Manufacturing Patents' independent claims involves a "chemically defined medium." The patents' specification defines the term, *e.g.*, '715 patent, 30:44-48, and that definition is controlling. As the Federal Circuit has explained, "[w]hen a patentee explicitly defines a claim term in the patent specification, the patentee's definition controls." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1380 (Fed. Cir. 2009).

Mylan's proposed construction adds to the specification's definition a second concept that resembles, but is not identical to, the specification's next sentence:

'715 patent, 30:47-51	**Mylan's Proposed Construction**
Chemically defined media do not contain bacterial, yeast, animal, or plant extracts, animal serum, or plasma, *although individual plant or animal-derived components (e.g., proteins, polypeptides, etc.) may be added*	. . . and does not contain bacterial, yeast, animal, or plant extracts *or hydrolysates*, animal serum, or plasma

Regeneron views adding the second sentence onto the Court's construction of CDM as unnecessary, but has no objection to appending it as it is written in the specification. Regeneron

objects, however, to Mylan's blatant rewriting of it and its omission of the sentence's exception.

As the italicization above makes clear, Mylan's construction differs from the patent in two important ways. First, the term "or hydrolysates" is not in the specification—Mylan simply added it. Second, Mylan's construction omits the sentence's exception that "individual plant or animal-derived components (e.g., proteins, polypeptides, etc.) *may be added*." By leaving out this clause, Mylan's proposal improperly forecloses the addition of plant or animal-derived components to a CDM, which the specification plainly contemplates.

Mylan's primary argument for rewriting the specification appears to be a definition from one of Regeneron's earlier-filed, "provisional" applications.[8] *See* ECF No. 102 at 6. But the Federal Circuit has made clear that it is "legally incorrect" to rely on such evidence in the face of an explicit definition in the issued patent. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1585 (Fed. Cir. 1996) ("Because the specification clearly and unambiguously defined the disputed term in the claim, reliance on this extrinsic evidence was . . . legally incorrect.").[9] Even if the provisional application was relevant, it militates *against* Mylan's construction. The sentences that Mylan cites from the provisional application—*e.g.*, "A CDM does not include hydrolysate such as, for example, soy hydrolysate," *see* ECF No. 102 at 6—were *omitted* from the Manufacturing Patents' specifications, which indicates that the patentee did *not* intend to limit the scope of "CDM" as Mylan proposes. The Federal Circuit encountered a similar

[8] A provisional application is, essentially, a rough draft for a patent application. It can establish a priority date, but it does not undergo patent examination and it need not contain various of the formalities of an actual patent application. *See generally* 35 U.S.C. § 111(b). The Manufacturing Patents cite to multiple provisional applications.

[9] Because the 62/944,635 provisional application was not incorporated by reference into the patents' specification, or discussed by the Examiner, it is extrinsic evidence. *See dunnhumby USA, LLC v. emnos USA Corp.*, 2015 WL 1542365, at *11 (N.D. Ill. Apr. 1, 2015).

situation in which the patentee's specification omitted the provisional application's statement that the invention was limited to "one-step operation." *MPHJ Tech. Investments, LLC v. Richo Ams. Corp.*, 847 F.3d 1363, 1368-69 (Fed. Cir. 2017). The Federal Circuit deemed this removal "to be significant" and held the claims were "not limited to single-step operation." *Id.* The same logic applies here—Regeneron's *removal* of the provisional application's statement about soy hydrolysate compels that the term "CDM" is *not* limited in the manner Mylan contends.

C. "Cell(s) Cultured in a Chemically Defined Medium (CDM)"

Regeneron's Proposed Construction	Mylan's Proposed Construction
Plain and ordinary meaning in view of the claims and specification; to the extent there is a dispute as to claim scope, this limitation does not exclude methods where the cell is subsequently cultured in a non-chemically defined medium	Plain and ordinary meaning: harvested from / a clarified harvest made using CDM (*i.e.*, a synthetic growth medium in which the identity and concentration of all the ingredients are defined and does not contain bacterial, yeast, animal, or plant extracts or hydrolysates, animal serum, or plasma)

All of the independent claims of the Manufacturing Patents include limitations containing the phrase "cell(s) cultured in a chemically defined medium (CDM)," which Mylan has identified for construction. Regeneron proposes that these "cultured" limitations be given their plain and ordinary meaning, consistent with the definition of "CDM," *see supra* IV.B. Mylan, by contrast, has offered a construction that departs from the claim language in two ways.

The first error in Mylan's proposed construction is its inclusion of a parenthetical characterizing the term CDM, which again adds a phrase that includes the words "or hydrolysates" and fails to acknowledge that plant-derived components may be added to a CDM. For the reasons discussed above, the Court should reject Mylan's proposed construction.

Even if Mylan were right regarding the "CDM" term—which it is not—there is a second error in its proposed construction of the "cultured" terms. Under Mylan's construction, the *harvest* must occur from a CDM. Because the harvest occurs at the end of the cell culture

process, Mylan's construction effectively requires that the *entire* cell culture must occur in a CDM. The claims, specification, and prosecution history make clear, however, that the cells only must be "cultured in a CDM" at *some point* during the cell culture process. The claims do not foreclose additional steps in which the cells are cultured in a non-CDM prior to the harvest.

Claim 1 of the '715 patent is exemplary and is reproduced in relevant part below:

> 1. A method of producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM), comprising:
> (a) providing a host cell genetically engineered to express aflibercept;
> (b) culturing said host cell in said CDM under conditions suitable in which said host cell express said aflibercept . . . ; and
> (c) harvesting aflibercept produced by said host cell.

Similar to the other claims at issue, claim 1 of the '715 patent recites a method of producing aflibercept "comprising" three steps. Those three steps clarify how to "produc[e] aflibercept harvested from a host cell cultured in [CDM]"—in particular, one must (a) "provid[e] a host cell genetically engineered to express aflibercept;" (b) "cultur[e] said host cell in said CDM" under certain conditions, and (c) "harvest[] aflibercept produced by said host cell."

There does not appear to be any dispute between the parties that step (b) of the '715 patent—as well as the similar CDM-related limitations of the other patents—requires that, at some point, the aflibercept-producing cell must be cultured in a CDM. Where the parties differ, however, is whether a defendant could escape infringement by adding a *subsequent* step in which the aflibercept is cultured (however briefly) in—and then harvested from—a non-CDM.

Dispositive to this dispute is that the claims use the word "comprising" to introduce the claimed steps. "Comprising" is a term of art in patent drafting and when used in a method claim, it means that the method can have additional steps. As the Manual for Patent Examining and Procedure ("MPEP") explains, claims are generally open or closed to additional steps or

elements. *See* MPEP 2111.03. "Consisting of" is a restrictive phrase—it "excludes any element, step, or ingredient not specified in the claim." *Id.* By contrast, "comprising" "is inclusive or open-ended *and does not exclude additional, unrecited elements or method steps*." *Id.* (emphasis added). Accordingly, Federal Circuit precedent makes clear that "comprising" is open-ended and should be read to mean "including but not limited to." *Game & Tech. Co., Ltd. v. Activision Blizzard Inc.*, 926 F.3d 1370, 1378 (Fed. Cir. 2019); *accord Cias, Inc. v. Alliance Gaming Corp.*, 504 F.3d 1356, 1360 (Fed. Cir. 2007) ("comprising" transition means "that the ensuing elements or steps are not limiting"); *Gillette Co. v. Energizer Holdings, Inc.*, 405 F. 3d 1367, 1371 (Fed. Cir. 2005) ("The word 'comprising' transitioning from the preamble to the body signals that the entire claim is presumptively open-ended.").

Mylan's proposed construction violates this well-established rule that "comprising" claims are open to additional elements. Cell cultures often involve a series of steps, in which the liquid in which the cells are cultured is changed by the addition of "feeds." Under Mylan's proposed construction, even if a cell culture process includes a step of "culturing said host cell in said CDM" with all of the specified components, a defendant could avoid infringement by using an *additional* step—later in the cell culture process—in which the cell is cultured in non-CDM. Such a construction is entirely inconsistent with the "comprising" claim language.

The Federal Circuit rejected the precise argument that Mylan now advances in *Invitrogen Corp v. Biocrest Mfg., LP*, 327 F.3d 1364 (Fed. Cir. 2003). The claim in that case covered "[a] process for producing transformable E. coli cells of improved competence by a process comprising" three steps, the first of which was "growing E. coli cells in a growth-conducive medium at a temperature of 18° C. to 32° C." *Id.* at 1366. The district court interpreted the claims to require that *all* cell growth must occur between 18° C. to 32° C. *Id.* at 1368 ("In other

words, the district court's claim interpretation foreclosed any growth other than growth in the claimed temperature range."). The Federal Circuit reversed, explaining that "[t]he transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps." *Id.* at 1368. As such, the court concluded that the claim did *not* preclude processes wherein growth *also* occurs outside the specified temperature range. *See id.* ("[C]laim 1 does not address and therefore permits growth before the steps disclosed in the claim at temperatures outside the range of 18° C to 32° C."). The present case is analogous—none of the claims at issue preclude processes where the cells are cultured in non-CDM *subsequent* to the claimed step in which they are cultured in CDM.

Mylan's construction also conflicts with other claim language. For example, claim 1 of the '715 patent recites, in relevant part, "[a] method of producing aflibercept harvested from a *host cell cultured* in a chemically defined medium (CDM), comprising . . . ." Each claim-at-issue likewise refers to "cell(s)" being "cultured." Those words are omitted from Mylan's construction, which instead seeks to require that the *harvest* be "made using CDM." However, the claims and specification consistently differentiate between the *culturing* step and the *harvesting* step, the latter of which occurs *after* the cells have been cultured. *See, e.g.*, '715 patent, claim 1 (step (b) "culturing said host cell" versus step (c) "harvesting aflibercept"); '715 patent, 22:8-13 ("In one embodiment, the method comprises *culturing* a host cell in a CDM under suitable conditions, wherein the host cell expresses a recombinant protein of interest, such as aflibercept, and *harvesting* a preparation of the protein of interest produced by the cell . . . ." (emphases added)), 54:43-45 (differentiating between a "cell culture fluid" and "harvested cell culture fluid"), 71:57-61 ("Th[e] invention includes culturing a host cell in a modified CDM under suitable conditions in which the cell expresses a recombinant protein . . . *followed by*

harvesting a preparation of the recombinant protein of interest produced by the cell." (emphasis added)). Mylan's construction departs from the plain language of the claims—which relates to how the cells are cultured—to instead impose a requirement on how the harvest is made.

The prosecution history further militates against Mylan's suggestion that the harvest must be made from CDM. During prosecution of the application that resulted in the '532 patent, the Examiner initially rejected the claims because they did "not state what is cultured in the CDM," observing that "a harvest is typically the product of a culturing step rather than the substance which is cultured." *See* Ex. 20, Non-Final Rejection at 3 (Nov. 3, 2021). To overcome that rejection, Regeneron amended the claims to make clear that it was the *cells*, not the harvest, that must be "cultured in a chemically defined medium (CDM)." *See* Ex. 21, Response to Non-Final Rejection at 3 (Dec. 16, 2021). Mylan's attempt to rewrite the claims—to require that the harvest be made using CDM—is inconsistent with this prosecution history.

In view of the claim language, specification, and prosecution history, these disputed terms should be given their plain and ordinary meaning, and the terms should not be read to exclude methods where the cell is subsequently cultured in a non-CDM.

V. Conclusion

For the foregoing reasons, the Court should adopt Regeneron's proposed constructions of the disputed claim terms and reject Mylan's proposals.

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CERTIFICATE OF SERVICE

I hereby certify that on November 29, 2022, I electronically filed the foregoing with the Clerk of the Court by using the Court's CM/ECF system. Counsel of record for all parties will be served by the Court's CM/ECF system.

/s/ Steven R. Ruby
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